UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/621,715	07/18/2003	Toshihiro Mori	0649-0963P	1567

2292 7590 01/07/2008

BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER	
KAPUSHOC, STEPHEN THOMAS	
ART UNIT	**PAPER NUMBER**
1634	

NOTIFICATION DATE	DELIVERY MODE
01/07/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/621,715	MORI ET AL.	
	Examiner	Art Unit	
	Stephen Kapushoc	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,10,12,13,15-20,23 and 24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,10,12,13,15-20,23 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 10, 12, 13, 15-20, 23 and 24 are pending and examined on the merits.

Please note: The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This Office Action is in reply to Applicants' correspondence of 10/05/2007.

Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put the application in condition for allowance. Any new grounds of rejection presented in this Office Action are necessitated by Applicants' amendments. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.

This Action is made **FINAL**.

Response to the Declaration Under 37 CFR 1.132 and Amendments to the Specificaiton

1. The Declaration under 37 CFR 1.132 filed 10/05/2007 has been considered.

The Declaration asserts that the specification as originally filed provides a mistranslation of the phrase at ¶[0063] of Publication No. 2004/0063122 (The US PG Publication of the instant application) from the Japanese priority document JP 210832/2002. Where the parenthetical phrase '(e.g. 10kb, or more preferably 30kb or longer)' is recited, the phrase should properly read '(e.g. 10kb or longer, or more preferably 30kb or longer)'. The Declaration has been considered and is acceptable evidence of the proper translation of the phrase from the priority document.

The amendment to the specification as presented 10/05/2007 is entered.

Interview

2. Applicants' reference (p.11 of Remarks) to the interview of 8/28/2007 is noted. The record of the interview is complete.

New Claim Objections

3. Claim 23 is objected to because of the following informalities:

Line 8 of claim 23 recited the phrase 'acids which does not', where the phrase 'acids which do not' is correct.

Line 15 of claim 23 recites the phrase 'between 2.5 µm to 10µm' where the phrase "between 2.5 µm and 10µm' is correct.

Appropriate correction is required.

Response to Remarks concerning Rejections Under 35 USC 103

4. Applicants have traversed (pages 11-15 of Remarks) the rejection of claims under 35 USC 103 as obvious in view of the teachings of Kitos et al (1973) in view of Tsao et al US Patent 4,090,022 (1978), as set forth in the previous Office Action.

Applicants have argued that the claims have been amended to require the specific limitation that a nucleic acid of 10kb or longer is adsorbed to a solid phase. It is noted that the instant Office Action provides new rejections addressing the obviousness of this limitation.

New Claim Rejections - 35 USC § 103

In the rejection of claims under 35 USC 103, the required limitations of the claimed methods are noted. The base claim (i.e. claim 1) has been amended to include the limitation that a nucleic acid of 10kb or longer is adsorbed from a nucleic acid sample solution. The rejected claims do not require, for example, selecting a length of a nucleic acid to be purified from a nucleic acid sample solution containing nucleic acids of different lengths, and selecting a rate of surface saponification and pore size of a triacetylcellulose film such that the saponification rate and pore size are suitable separation and purification of the said nucleic acid to be purified.

5. Claims 1, 10, 16 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kitos et al (1973) in view of Tomida et al (1993) and Tsao et al US Patent 4,090,022 (1978).

Kitos et al teaches separation of nucleic acids using solid phase cellulose (p.5807, left col., lns.13-25).

Regarding claim 1 Kitos et al teaches adsorbing nucleic acid, to a solid phase of cellulose wherein a nucleic acid solution contains nucleic acids of different lengths (Table 1; p.5807, left col., lns.41-62). Kitos further teaches washing the solid phase (p.5807, left col., lns.26-30; Figure 1 legend) and desorbing the nucleic acid (p.5807, left col., lns.37-40; Figure 1 legend). Kitos teaches the purification of the nucleic acid from the mixture (see for example Table 1, last data row, where [^{3}H]poly(A) in a mixture of poly(A0) and poly(U) is eluted in Buffer K.

Regarding claim 16, Kitos et al teaches elution buffer having a salt concentration lower than 0.5M (p.5807, left col., lns.37-40).

Regarding claim 17, Kitos et al teaches chromatography using a cellulose in a column (p.5807, left col., lns.15-25), which is a unit having two openings (at the top and the bottom) that contains the solid phase.

Kitos et al does not specifically teach adsorbing a nucleic acid of 10kb or longer.

Tomida et al teaches the analysis of nucleic acids in tissues, including the specific analysis of nucleic acids of 10kb or longer (e.g. p.195 – Cloning of cDNA encoding soluble D-factor receptor).

Neither Kitos et al nor Tomida et al teach the use triacetylcellulose with a surface saponification of 10-100% and a pore size of 0.1 μm to 10 μm.

Tsao et al teaches porous cellulose beads for the separation of nucleic acids (col.2 lns.26-28 and lns.51-53).

Regarding the limitations of claim 1, Tsao et al teaches that beads may have pore sizes ranging from 0.05 to 30 μm (col.7 lns.17-18), and specifically that pore sizes of beads can be 1,000 Angstroms (col.3 lns.47-51) which is 0.1 μm. Tsao also teaches (col. 11 – Example V) using beads made from cellulose triacetate where the beads are treated with 0.15 N sodium hydroxide overnight at room temperature (as in col.10 Example I), where such a treatment results in a porous bead with a center of cellulose triacetate and a surface of cellulose triacetate having 10 to 100% saponification (i.e. saponification is deacetylation of the cellulose) on the surface.

Regarding claim 10, the procedure of Tsao et al of creating a cellulose triacetate bead followed by deacetylation results in saponified triacetylcellulose coated on a bead of cellulose triacetate.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the porous beads made of cellulose triacetate taught by Tsao et al for the purification of nucleic acids using the methods taught by Ktios et al. One would have been motivated to use the beads of Tsao et al because Tsao et al teaches that such beads offer enhanced flow properties (col.11 lns.24-44) and Kitos et al uses column based methods that require fluid flow. It would have been further obvious to adsorb the nucleic acid from the sample taught by Tomida et al, which comprises the required 10kb nucleic acid because Tomida et al teaches the purification of the analysis of the 10kb nucleic acid in a mixture of nucleic acids (e.g. p.193 - Isolation of total RNA; where a total RNA mixture comprises nucleic acids of different lengths including the 10kb nucleic acid of interest). One would have been motivated to purify the 10kb nucleic acid of Tomida based on the teaching of the analysis of that nucleic acid by Tomida (p.194 – Northern blot analysis), and the teachings of Kitos et al that it is possible to separate poly(A)-containing RNA from a nucleic acid mixture using cellulose adsorption (p.5091, left col., last ¶).

6. Claims 12, 15, and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kitos et al (1973) in view of in view of Tomida et al (1993) and Tsao et al US Patent 4,090,022 (1978) and further in view of Woodard et al (EP 0512767).

The teachings of Kitos et al in view of in view of Tomida et al and Tsao et al are applied to claims 12, 15, and 18 as they were previously applied to claims 1, 10, 16, 17,.

Kitos et al in view of Tsao et al teaches the separation of a nucleic acid from a solution containing a mixture of nucleic acids using porous surface-saponified cellulose triacetate.

Kitos et al in view of Tao et al does not teach making a sample solution with organic solvents ad solubilizing reagents (claim 12), wash buffers with alcohols (claim 15), or a pressure difference generating apparatus (claim 18).

Regarding claim 12, Woodard et al teaches a steps of treating a sample containing a cell or a virus with a nucleic acid solubilizing reagent (i.e. a lysis buffer) and then preparing the sample solution by adding an aqueous organic solvent to the solution. Specifically, Woodard et al teaches that DNA is obtained in such a way that the procedure ends with a suspension of DNA in a solution such as a lysate, a step which includes treating the sample with a solubilizing reagent (p. 3, lines 3-13). Woodard et al also teaches the subsequent addition of an organic solvent to the solution (p. 3, lines 19-22).

With regard to claim 15, Woodard et al teaches the nucleic acid washing buffer that contains 50% ethanol, for example (p. 3, line 24).

With regard to claim18, Woodard et al teaches the use of a unit with a blotter which 'pulls liquid through a membrane' (p. 9, lines 5-15).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the methods of Woodard to provide nucleic acid and apparatus of Woodard in the separation of nucleic acids according to the methods of Kitos et al in view of Tsao et al. One would have been motivated to use the

reagents and methods of Woodard et al based on the teachings of that such methods can successfully purify nucleic acids, and the teachings of Kitos et al that such nucleic acids may be purified form cellular sources (p.5091, right col., last paragraph).

7. Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kitos et al (1973) in view of in view of Tomida et al (1993), Tsao et al US Patent 4,090,022 (1978) and Woodard et al (EP 0512767), and in further view of Benjamin et al US Patent 5,695,946.

The teachings of Kitos et al in view of in view of Tomida et al, Tsao et al and Woodard et al are applied to claim 13 as they were previously applied to claims 12, 15, and 18.

Woodard et al teaches using "typical" procedures for obtaining DNA from samples (p. 3, lines 5-6), but does not teach a step wherein the nucleic acid solubilizing reagent comprises a guanidine salt, a surfactant, and a proteolytic enzyme.

Benjamin et al teaches that target nucleic acid molecules are released from cells by treatment with any number of reagents, including guanidine salts, proteinase K and detergents (Col. 8, lines 7-12). Benjamin et al exemplifies the use of the surfactant SDS for cell lysis (Col. 12, line 15).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have have modified the methods of Kitos et al in view of Tsao et al and Woodard et al, so as to have utilized a lysis buffer that included reagents that are typically considered lysis agents for the release of nucleic acids from sample

cells. One would have been motivated by the teachings of Woodard et al that any such typical methodologies for obtaining lysis solutions could be used and by the teachings of the Benjamin et al that each of these reagents are commonly used for the lysis of cells.

8. Claims 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kitos et al (1973) in view of in view of Tomida et al (1993), Tsao et al US Patent 4,090,022 (1978) and Woodard et al (EP 0512767), and in further view of Heath WO 99/13976.

The teachings of Kitos et al in view of in view of Tomida et al, Tsao et al and Woodard et al are applied to claims 19 and 20 as they were previously applied in the rejection of claims 12, 15, and 18 previously in this Office Action.

Heath teaches methods for isolation of nucleic acid from samples and teaches automated steps of loading a sample into a container with at least two openings (p. 7, lines 11-12), loading a wash into the container (p. 7, lines 13-17), and loading desorbing buffer (referred to as elution buffer) into the container (p. 7, lines 18-23). Heath teaches the use of vacuum pumps for the movement of solutions into and out of the isolation chamber (p. 8, lines 6-14; 21-22). Heath specifically teach that methods in which the sample is loaded via aspiration which occurs via the insertion of the opening of the chamber into the sample and the application of negative pressure to suck the sample into the chamber (p. 10, exemplified p. 23). Further, Heath teaches methods in which the gases are pumped into the chamber which increases pressure in the chamber and forces fluid out of the chamber (p. 12, lines 13-15).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods of Kitos et al in view of Tsao et al and Woodard et al, to include the sample processing methodologies taught by Heath. One would have been motivated to apply the methods of Heath to the methods taught by Kitos et al in view of Tsao et al and Woodard et al in order to have provided methods for applying the fluids necessary to practice the methods taught Kitos et al in view of Tsao et al and Woodard et al to the solid supports for the isolation of nucleic acids.

Maintained Claim Rejections - 35 USC § 112 1st ¶

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1, 10, 12, 13, 15-20, 23 and 24 are rejected under 35 U.S.C. 112, first paragraph, because the specification is enabling for some amount of separation of nucleic acids having lengths of 2kb or shorter from nucleic acids having lengths of 10kb or longer, using porous surface saponified triacetylcellulose with a particular saponification rates and pore sizes, such as:

> A method for separating and purifying nucleic acids having a length of 2 kb or shorter and nucleic acids having a length of 10 kb or longer from a nucleic acid sample solution comprising said nucleic acids, which comprises the following steps performed in the following order:
>
> (i) adsorbing a nucleic acid mixture comprising nucleic acids having lengths of 2 kb or shorter and comprising nucleic acids having lengths of 10 kb or longer to a first solid phase, wherein the first solid phase comprises a porous film of surface-saponified triacetylcellulose having a surface saponification rate of 50% and a pore size between 0.1 μm and 0.2 μm;

(ii) collecting nucleic acids which do not adsorb to the first solid phase to obtain a first flow through fraction;

(iii) washing the first solid phase using a nucleic acid washing buffer;

(iv) desorbing the nucleic acids adsorbed to the first solid phase by using a liquid capable of desorbing the nucleic acids adsorbed to the solid phase, thereby obtaining purified and separated nucleic acids having a length of 10 kb or longer;

(v) adsorbing the first flow through fraction to a second solid phase, wherein the second solid phase comprises a porous film of surface-saponified triacetylcellulose having a surface saponification rate of 100% and a pore size of between 1 μm and 2.5 μm;

(vi) collecting nucleic acids which do not adsorb to the second solid phase to obtain a second flow through fraction;

(vii) adsorbing the second flow through fraction to a third solid phase, wherein the third solid phase comprises a porous film of surface-saponified triacetylcellulose having a surface saponification rate of 100% and a pore size of between 0.2 μm and 0.4 μm;

(viii) washing the third solid phase using a nucleic acid-washing buffer; and

(ix) desorbing the nucleic acids adsorbed to the third solid phase by using a liquid capable of desorbing the nucleic acid adsorbed to the third solid phase, thereby obtaining purified and separated nucleic acids having a length of 2 kb or shorter.

The specification does not reasonably provide enablement for the separation of a 10 kb or longer nucleic acid from any nucleic acid mixture using the broadly recited pore sizes and saponification rates recited in the instant claims and disclosed in the specification. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Nature of the invention and breadth of the claims

The nature of the invention is a method for separating and purifying a nucleic acid of 10kb or longer from a mixture of nucleic acids using a porous membrane comprising surface saponified triacetlycellulose. Alteration of the surface saponification rate of acetylcellulose and the size of the pores in a film made from the compound

allows for the adsorbing of particularly sized nucleic acids, and their subsequent purification by desorbing. The nature of the invention requires knowledge of the relationship of the surface saponification rate and pore size of a film of cellulose triacetate with recovery rate of any particular length of nucleic acid.

The claims encompass the separation and purification of any type of nucleic acid (e.g. DNA or RNA) from a nucleic acid mixture of any complexity (i.e. containing any amount of nucleic acids of any length). The claims encompass the use of any surface saponification rate between 10 to 100%, and any pore size between 0.1 μm to 10 μm.

State of the prior art, level of skill, and level of unpredictability

While the level of skill in the art of nucleic acid separation is high, the state of the prior art with regard to nucleic acids binding to acetylcellulose indicates a high level of unpredictability. The prior art does not teach any correlation between particular saponification rates or pore sizes and the ability of an organic macromolecule to separate nucleic acids of specific lengths from mixtures of nucleic acids.

Several references teach that cellulose acetate membranes will not bind to DNA. GE Osmonic (1997) teaches the use of cellulose acetate membranes to filter nucleic acid probes, indicating the membrane is ideal because it is a non-DNA binding polymer. Similar statements about cellulose acetate are taught in two recent references: Corning (2005) indicates that cellulose acetate is inert, and does not bind either DNA or protein, and Whatman (2005) indicates that ability of DNA to bind to cellulose acetate is 'very low'.

It is also unpredictable how the sequence of any particular DNA might affect its ability to be separated in a size dependant manner using the methods described by the instant specification. Yang et al (1998) teach that DNA molecules with particular sequences (Table 1, p.5465) can bind tightly and specifically to cellulose. It would therefore be unpredictable how the presence of any of the indicated 'cellulose-binding DNA aptamer' sequences, within a larger nucleic acid sequence, would affect the separation of the nucleic acid by the method of the instant application regardless of the saponification rate or pore size of a medium containing an organic macromolecule with hydroxyl groups.

Van Oss et al (1987) indicate the unpredictability of different nucleic acids (e.g. DNA versus RNA) binding to acetylcellulose. The reference teaches that while interaction between DNA and cellulose esters can be considerable, the binding energy of RNA to cellulose esters is low (p.53). Table IV (p.60) indicates the clear difference in free energy of adhesion of DNA on cellulose acetate versus RNA on cellulose acetate; the reference teaches that DNA should bind more strongly to cellulose esters that RNA (p.61), and RNA is much more weakly attracted to cellulose esters than DNA (p.63). Pan et al (2003) teaches the inherently different structural properties of DNA versus RNA. The reference indicates that different chemistries of DNA and RNA allow for different flexibilities and the adoption of different conformations, thus making it unpredictable as to how these different molecules would interact with the membranes (i.e. varying saponification rates and pore sizes) discussed in the instant application.

Direction provided and presence of working example

The instant specification asserts that nucleic acids can be separated and purified by preparing a plurality of porous membranes with varying surface saponification rates and varying pore sizes. The specification provides data regarding the recovery rate of two DNA fragments (1.3kb and 48kb) from various preparations of triacetylcellulose (p.28, Tables 3 and 4; Fig 5). The specification teaches that recovery rate (that is the percentage of the DNA that is applied to a membrane which is adsorbed to the membrane and then desorbed from the membrane) varies between two different saponification rates (either 50% or 100%) and four different pore sizes (0.2, 0.4, 1.0, or 2.5μm). There is no other information provided for any other saponification rates or pore sizes. Notably, there is no information contained within the specification for saponification rates lower than 50% (as are encompassed by the claims, for instance claims 4 and 5 which particularly point out saponification rates with lower limits of 5% and 10%, respectively). Similarly, there is no other information provided for any pore size other than those listed in Table 1; notably there is no information in the specification concerning pore sizes larger than 2.5μm (as are encompassed by the claims, for instance claim 9 which particularly points out pores sizes as large as 10μm).

The specification indicates (pp.10-11) the following saponification rates combined with the following pore sizes will allow the recovery (by adsorbing and subsequently desorbing) of particularly sized DNA: both low molecular weight DNA and high molecular weight DNA were recovered from 100% saponified membranes with 0.2μm pores; recovery of high molecular weight DNA is relatively higher (compared to recovery of low molecular weight DNA) from 50% saponified membranes with 0.2μm pores; the

recovery rate of high molecular weight DNA is high from 100% saponified membranes with 2.5μm pores.

The specification provides a single example of the purification of a low molecular weight nucleic acid and a high molecular weight nucleic acid from a nucleic acid mixture (pp.28-29). This example demonstrates the separation of a 1.3kb fragment from a 48kb fragment which had been mixed together in an aqueous solution. In the example, the different DNAs are separated by the sequential action of a first membrane (100% saponified, 0.2 μm pore size) and a second membrane (50% saponified, 0.2 μm pore size). And while the specification asserts that it is clear from the results of Fig. 5 (a photograph of an agarose gel) that a nucleic acid having a desired size can be purified by selecting saponification rate and pore size, there is no quantification of the results to indicate the resulting level of separation. For instance, regarding the isolation of the 1.3kb DNA (condition (c) on p.29) from a mixture containing 10μg each of a 1.3kb DNA and a 48kb DNA (as in (4) on p.27), one would expect (based on the collection rate information presented in Tables 3 and 4) for the final recovered product to contain 7.7μg of 1.3kb DNA and 1.4μg of 48kb DNA.

The specification does not provide any example of the separation of any other nucleic acid mixtures other that the 1.3kb and 48kb mixture described in Example 1, or results concerning recovery rates from any other saponification rates or pore sizes than those presented in Tables 3 and 4. It is unknown what resolution of separation would be attainable with other membrane and/or nucleic acid mixture conditions. For instance, are there any possible conditions that would allow for the separation of a 9kb DNA

fragment from an 11kb DNA fragment. Additionally, while the specification refers to conditions for purification of high molecular weight versus low molecular weight molecules, the specification refers to a 10kb fragment as both a relatively long nucleic acid (p.12 ln.1) and a relatively short nucleic acid (p.12 ln.11).

The specification does not provide any guidance concerning the separation of any nucleic acid mixtures containing anything other than the double stranded DNA of Example 1.

11. Particularly relevant to newly presented claims, the specification does not support the required method steps of claims 23 and 24. For example, lines 4-12 of claim 23 require that nucleic acids of 2kb or shorter are desorbed from a film with a saponification rate of 50%. However the instant specification teaches that shorter nucleic acids are adsorbed less efficiently to a 50% saponified film than longer nucleic acids (Tables 3 and 4). Similarly, claim 24 lines 4-11 requires that longer nucleic acids are separated by collecting nucleic acids that do not absorb to any of the broadly recited films with a saponification rate of 10% to 100% and a pore size between 0.1um and 10um. However, the specification does not disclose any particular saponification rate or pore size conditions in which a flow through fraction (i.e. nucleic acids that do not adsorb) specifically contain more longer nucleic acids than shorter nucleic acids (Tables 3 and 4).

Quantity of experimentation required

A prohibitive amount of experimentation would be required to use the claimed invention in its full scope. For any given mixture of nucleic acids, one would have to

establish the recovery rate of a nucleic acid of interest having a particular length under different saponification and pore size conditions. One would also have to determine if the described methods would be compatible RNA, or perhaps with other types of nucleic acids such as peptide nucleic acids (PNA).

Alteration of saponification rate alone would require a large quantity of experimentation. The specification indicates conditions used to achieve either 50% or 100% saponification (p.26), however there is no way to predict what conditions are needed to achieve any other saponification rates (e.g. what concentration of sodium hydroxide solution to use, and how long to treat a membrane). The specification only indicates that altering sodium hydroxide concentration can change saponification rate (p.10), and that the rate is determined by quantifying remaining acetyl groups by NMR.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and scope of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the lack of guidance by the applicant and the lack of a working examples, it is the conclusion the an undue amount of experimentation would be required to use the invention in the full scope of the claims.

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 112 1st ¶ paragraph (pages 16-17 of the Remarks). Applicants' arguments and amendments to the claims have been fully and carefully considered but are not found to be persuasive.

Initially Applicants assert that in the interview of 8/28/2007 the Examiner stated the belief that there was enablement support for separation of nucleic acids having a length of 2kb or less and/or nucleic acids having a length of 10 kb or more, either individually or in a mixture. More precisely, the Examiner stated that there was support in the specification for specification conditions (i.e. saponification rates and pore sizes) that could separate and purify a nucleic acid of 10kb or longer from a nucleic acid of 2kb or shorter in a mixture containing the two nucleic acids. It was urged that in the rejection of claims for lack of enablement the issue is the resolution of separation that Applicants have enabled, where for example the pending claims encompass the separation and purification of a 10kb or longer nucleic acid for a sample comprising nucleic acids of any different lengths.

The examiner maintains that the claims require the separation and purification of a nucleic acid of 10kb or longer from a sample solution 'wherein the solution contains nucleic acids of different lengths', and the claims thus encompass the separation of the recited 'nucleic acid having a length of 10 kb or longer' from a solution containing any sized nucleic acids. Applicants Examples (from the filed specification and the Declaration) demonstrate only the separation of nucleic acids in a mixture containing short nucleic acids (200 bp, or 1,300 bp, or 1,500 bp) from very long nucleic acids (48,000 bp). Thus Applicants characterization of the examples as teaching 'how to separate both low molecular fragments and high molecular weight fragments' and providing evidence for separations 'over three orders of magnitude of size range' does not serve to address the requirements of the claimed method.

With regard to newly presented claims 23 and 24, as specifically detailed in the rejection above (see the above paragraph number 11) the required separation steps of the claims do not appear consonant with the teachings of the specification. The beginning of this rejection (see paragraph number 10 above) provides a potential claim in the style of newly presented claim 23 with separation steps that are consistent with the teachings of the specification (e.g. Table 3 and 4, and pages 28-29).

The rejection as set forth is **MAINTAINED.**

Conclusion

12. No claim is allowed

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

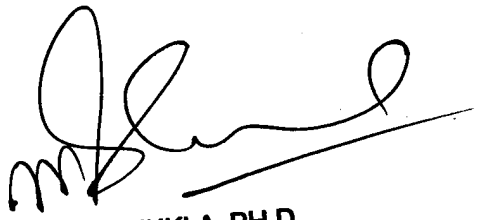
Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem

with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days.

Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Stephen Kapushoc/
Art Unit 1634



RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER